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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,943	03/28/2001	Ulf Eriksson	1064/48487	9621

23911 7590 12/20/2001

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1633	4

DATE MAILED: 12/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,943	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Priority to provisional application 60/192,507 filed on 3/28/00 is acknowledged. However, examples 8-11 on pages 30-31 of application no. 09/818,843 do not enjoy priority to this date because there is not written support in the provisional for these examples.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claim 1 is objected to because of the following informalities: the abbreviation PDGFC should be preceded by platelet-derived growth factor-C. Appropriate correction is required.

Claims 1-24, to which the following grounds of rejection are applicable, are pending examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24, as best understood, are readable on a genus of a nucleotide sequences comprising a PDGF-C polypeptide or an analog thereof, or a functional fragment of PDGF-C polypeptide or an analog thereof, wherein the genus of the nucleotide sequences are not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of nucleotide sequences comprising a PDGF-C polypeptide or an analog thereof, or a functional fragment of PDGF-C polypeptide or an analog thereof. The as-filed specification provides sufficient description of a species of nucleotide sequences encoding a PDGF-C polypeptide set forth in SEQ ID NO: 1.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of nucleotide sequences comprising a PDGF-C polypeptide or an analog thereof, or a functional fragment of PDGF-C polypeptide or an analog thereof as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of nucleotide sequences encoding an analog of PDGF-C or a functional fragment of PDGF-C or an analog the functional

fragment that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of nucleotide sequences comprising a PDGF-C polypeptide or an analog thereof, or a functional fragment of PDGF-C polypeptide or an analog thereof. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified analogs of the PDGF-C polypeptide and/or functional fragments thereof, and/or an analog of the functional fragment of PDGF-C set forth in SEQ ID NO: 1 that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed nucleotide sequences comprising analogs of PDGF-C or a functional fragment of PDGF-C and/or an analog thereof that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method for producing a transgenic mouse over expressing platelet-derived growth factor-C (PDGF-C) in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a pro-nuclei of a fertilized oocyte and implanting said fertilized oocyte into a pseudopregnant mouse; 2) A method for producing a transgenic mouse over expressing PDGF-C in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a mouse embryonic stem cell and injecting said embryonic stem cell into a developing mouse embryo; 3) A transgenic mouse whose genome comprises a PDGF-C polypeptide, wherein said PDGF-C polypeptide is over-expressed, wherein the overexpression of PDGF-C protein in cardiac cells of mouse results in said transgenic mouse exhibiting conditions of: (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild

type mouse; 4) A progeny from the transgenic mouse of 3, wherein the progeny displays a phenotype (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse; 5) A method for identifying a compound as a PDGF-C antagonist, said method comprising the steps of: a) isolating a cardiac cell from the mouse of 3, b) introducing said compound into the isolated cell from the transgenic mouse of 3, b) monitoring gene expression of PDGF-C in said cell compared to normal gene expression of PDGF-C in an isolated cell from a wild-type mouse, c) comparing gene expression in said mouse with gene expression in a control transgenic mouse d) identifying a compound that decreases the gene expression of PDGF-C; and thereby identifying said compound as a PDGF-C antagonist; 6) A method for screening a compound for inhibition of hypertrophy, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse, c) identifying a compound that decreases hypertrophy in said transgenic mice compared to the control mouse and the wild-type mouse; and thereby identifying said compound as an inhibitor of hypertrophy; 7) A method for screening a compound for inhibition of fibrosis, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse over-expressing PDGF-C, c) identifying a compound that decreases fibrosis in said mouse compared to the control transgenic mouse and the wild type mouse; and thereby identifying said compound as an inhibitor of hypertrophy, and

does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a nucleotide sequences comprising an analog of a PDGF-C polypeptide, or a functional fragment of a PDGF-C polypeptide or an analog thereof), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. for use in a method for producing a transgenic non-human mammal over-expressing PDGF-C.

The specification discusses that the invention features a genus of transgenic non-human mammals, which over-expresses PDGF-C and goes on to contemplate that there are two techniques for producing the transgenic mammals (page 9, lines 25-31). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection (page 20). In addition, the as-filed

specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA (pages 21-23).

The specification requires that the starting material, which is a nucleic acid encoding a PDFG-C polypeptide or functional fragment thereof, be used in a method of making a transgenic non-human mammal comprising of over-expressing PDGF-C. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (pages 20-22). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) A vector comprising the cDNA encoding PDGF-C and injected the vector into a male pro-nuclei of fertilized mouse oocytes (pages 23-24). The injected fertilized oocytes were implanted into pseudopregnant foster mothers (page 24). Furthermore, the disclosure provides sufficient characterization of mice over-expressing PDGF-C (pages 24-30). The heart phenotype of the transgenic mice was an expansion of the cardiac interstitium, which results in myocardial hypertrophy and fibrosis (page 26). The specification contemplates that the transgenic mice can be used in a method for identifying PDGF-C antagonist, compounds that inhibit hypertrophy, and compounds that inhibit cardiac fibrosis (pages 30-31).

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. See pages 20-23 of the specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as

exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Heprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than mice, the state of the

art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic mammals for use in over-expressing PDGF-C. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any method of producing transgenic mammals over-expressing PDGF-C other than transgenic mice. However, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence encoding the PDGF-C polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any other transgenic non-human mammal than in transgenic mice.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic mammal comprising a transgenic sequence encoding PDGF-C, which over-expresses the transgenic sequence such that a phenotype occurs other than in mice. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic mammal of the invention other than mice. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic mammal over-expressing PDGF-C other than mice.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth,

the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mammal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. PDGF-C) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic mammals other than transgenic mice. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammal comprising a transgene of interest (e.g. PDGF-C); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. PDGF-C) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of

genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic mammal using microinjection of transgene into germ line and producing a transgenic mammal which comprises a transgenic sequence encoding PDGF-C and which over-expresses the protein in the transgenic mammal, and, thus, a specific resulting phenotype other than in mice.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-

acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic mammal that over-expresses PDGF-C, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic mammal comprising a transgenic sequence encoding a PDGF-C polypeptide and which over-expresses the protein in the transgenic mammal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype other than in mice.

Furthermore, with respect to claims 1-24, which are directed to a PDGF-C polypeptide or an analog thereof, or an analog of a functional fragment used in a method for producing a transgenic mouse, which over-expresses PDGF-C, the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use an analog thereof. The as-filed specification provides sufficient guidance for one skilled in the art to make and/or use a nucleic acid encoding the PDGF-C polypeptide set forth in SEQ ID NO: 1. However, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be enabled to reasonably correlate SEQ ID NO: 1 to a nucleic acid encoding SEQ ID NO: 2 and any other nucleic acid sequence with sequence similarity to SEQ ID NO: 2, since at the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas. The state of the art in 1998, exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, Chiu

displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of an analog of PDGF-C or functional fragment thereof) as recited in the claims, particularly in view of the reasons set forth above and the breadth of the claims, one skilled in the art would not have known how to make and use the claimed invention so that it would operate as intended, *e.g.* said transgenic nucleic acid encoding a PDGF-C protein for use in a method of producing a transgenic mouse that over-expresses PDGF-C.

In addition with respect to claim 1, wherein in view of the breadth of the claim, the term cell encompassing any cell (e.g. somatic, embryonic, and germ-line) and introducing the cell into any target site in a mouse. The state of the art, as discussed above, teaches how to use a mouse pro-nuclei or a mouse embryonic stem cell in a method of producing a transgenic mouse, however the state of the art does not provide sufficient guidance for how to use any other cell (somatic cell, e.g. lung cell, muscle cell) in a method of producing a transgenic mouse. Furthermore, the state of the art teaches that stem cells are injected into a blastocyst or a mice embryo or that a pro-nuclei cell is injected into a fertilized oocyte, however, the disclosure and the art of record do not provide sufficient guidance for how to introduce a cell into any part of a non-human

animal other than injecting a pro-nuclei cell into a fertilized oocyte or a blastocyst. Thus, in view of the breadth of the claim the disclosure is only enabled for injecting a pro-nuclei of a mouse into a fertilized oocyte or injecting a genetically modified mouse embryonic stem cell into a blastocyst of a developing embryo of a mouse.

Furthermore, with respect to claim 1, which encompasses introducing a transgenic DNA into a cell of a mouse, the as-filed specification provides sufficient guidance for one skilled in the art to make and/or use a transgenic DNA operably linked to a promoter. However, the as-filed specification and the state of the art lack sufficient guidance for one skilled in the art to reasonably extrapolate from using a transgenic DNA operably linked to a promoter to a transgenic gene by itself for use in method of producing a transgenic mouse, which over-expresses PDGF-C. One skilled in the art for producing transgenic mouse would reasonably understand that a promoter operably linked to a transgenic DNA is required for producing a desired expression pattern of PDGF-C in cardiac cells. Furthermore, depending on any endogenous promoter in a mouse for the expression of PDGF-C would results in an undue amount of experimentation for one skilled in the art due to the random integration of transgenic DNA, the unpredictability of homologous recombination, and the gene targeting in producing transgenic mouse. Thus, in view of the art of record and the lack of sufficient guidance provided by the specification, the disclosure is not enabled for making or using a transgenic DNA encoding PDGF-C in method of producing a transgenic mouse, which over-expresses PDGF-C.

Furthermore, with respect to claims 20-21, which are directed to a method for identifying compounds as a PDGF-C antagonist, the specification and does not provide

sufficient guidance for one skilled in the art to monitor the biological activity of PDGF-C in said transgenic mouse. In view of the art of record and the disclosure, one skilled in the art would reasonably be enabled for monitoring the biological activity of PDGF-C by isolating a cell from a transgenic mouse and comparing the expression of mRNA or DNA to a cell isolated from a wild-type mouse and a cell isolated from a control transgenic mouse to determine the biological activity of PDGF-C in the transgenic mouse. However, the specification and art of record do not provide sufficient guidance for one skilled in the art to reasonably correlate in vitro assays to in vivo assays without an undue amount of experimentation. The specification lacks sufficient guidance for one skilled in the art to monitor the biological activity of PDGF-C in vivo in a transgenic mouse without isolating a cell from the mouse and comparing to other isolated cells. Thus, the claims are only enabled for a method for identifying a compound as a PDGF-C antagonist, wherein the method is an in vitro diagnostic assay.

Furthermore, with respect to claims 22, which is directed to an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the effect of a compound in a cell from a transgenic mouse over-expressing PDGF-C, the as-filed specification provides sufficient guidance for one skilled in the art to assay the cardiac effect of said compound. However, in view of the breadth of the claim, the as-filed specification lacks sufficient guidance for one skilled in the art to assay for any other effect. The specification provides sufficient guidance for one skilled in the art to identify a compound as a PDGF-C antagonist by assaying the cardiac effect of said compound on cardiac cells, but it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a cardiac effect to any other effect of a compound in any

other cell. The specification does not provide sufficient guidance for what other effects (e.g. neurological) could reasonably be observed without undue experimentation. Thus, the disclosure is only enabled for one skilled in the art to make and/or use an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the cardiac effect of a compound in a cardiac cell from a transgenic mouse over-expressing PDGF-C.

Thus, in view of the In re Wands' Factors, the disclosure is only enabled for: 1) A method for producing a transgenic mouse over expressing platelet-derived growth factor-C (PDGF-C) in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a pro-nuclei of a fertilized oocyte and implanting said fertilized oocyte into a pseudopregnant mouse; 2) A method for producing a transgenic mouse over expressing PDGF-C in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a mouse embryonic stem cell and injecting said embryonic stem cell into a developing mouse embryo; 3) A transgenic mouse whose genome comprises a PDGF-C polypeptide, wherein said PDGF-C polypeptide is over-expressed, wherein the overexpression of PDGF-C protein in cardiac cells of mouse results in said

transgenic mouse exhibiting conditions of: (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse; 4) A progeny from the transgenic mouse of 3, wherein the progeny displays a phenotype (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse; 5) A method for identifying a compound as a PDGF-C antagonist, said method comprising the steps of: a) isolating a cardiac cell from the mouse of 3, b) introducing said compound into the isolated cell from the transgenic mouse of 3, b) monitoring gene expression of PDGF-C in said cell compared to normal gene expression of PDGF-C in an isolated cell from a wild-type mouse, c) comparing gene expression in said mouse with gene expression in a control transgenic mouse d) identifying a compound that decreases the gene expression of PDGF-C; and thereby identifying said compound as a PDGF-C antagonist; 6) A method for screening a compound for inhibition of hypertrophy, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse, c) identifying compound that decreases hypertrophy in said transgenic mice compared to the control mouse and the wild-type mouse; and thereby identifying said compound as an inhibitor of hypertrophy; 7) A method for screening a compound for inhibition of fibrosis, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse over-expressing PDGF-C, c) identifying compound that decreases fibrosis in said mouse compared to the

control transgenic mouse and the wild type mouse; and thereby identifying said compound as an inhibitor of hypertrophy.

In conclusion, in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material, a transgenic non-human mammal over-expressing PDGF-C, the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human mammal other than mice, the claimed invention is only enabled for 1-7 listed above. Furthermore, the working examples for the demonstration or the reasonable correlation to the production of any transgenic mammal other than mice, in particular when the expression of the PDGF-C must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species other than mice, and the breadth of the claims drawn to any transgenic non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 3, 10-17, 20, and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the pro-nuclei" on page 32. There is insufficient antecedent basis for this limitation in the claim. There are several kinds of pro-nuclei cells well known in the art of transgenics and the claim does not define, which pro-nuclei is be referring to.

Claim 3 recites the limitation "the genomic DNA" on page 32. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites the limitation "the biological activity" on page 34. There is insufficient antecedent basis for this limitation in the claim.

Claim 22 recites the limitation "the effect" on page 34. There is insufficient antecedent basis for this limitation in the claim.

Claims 23 and 24 recite the limitation "the cardiac development" on page 35. There is insufficient antecedent basis for this limitation in the claim.

The statement in claims 10-17, "**an animal according to claim**" is indefinite because it does not point out which animal **an** animal is referring to in the claim. The dependent claim should state "**the** animal of claim."

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in

Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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December 14, 2001

DAVE T. NGUYEN
PRIMARY EXAMINER